Topics in Primary Care Medicine

Urethritis in Men

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Urethritis is a clinical syndrome characterized by a urethral discharge, urethral discomfort, or both, exacerbated by urination. It is a common outpatient complaint and a major public health problem. Urethritis is a sexually transmitted disease of moderate infectivity, requiring the tracing and treatment of case contacts. Control of the ongoing epidemic will depend upon more rigorous application of this epidemiological principle.

Causes

Two organisms have an established etiologic role in urethritis—*Neisseria gonorrhoeae* and *Chlamydia trachomatis*. *Ureaplasma urealyticum* has been implicated by strong circumstantial evidence, but its definitive etiologic role remains questionable.

Neisseria gonorrhoeae is a Gram-negative, kidney bean-shaped diplococcus that was first described in 1879. In the United States the current yearly case rate of gonococcal infections is estimated at 500 cases per 100,000 population, many of which present as urethritis. Certain groups have an increased risk for contracting gonococcal infections. Black men under 25 years of age of lower socioeconomic status account for approximately 60 percent of reported cases of gonorrhea. Gonococcal urethritis peaks during the summer months, and risk of infection is proportional to the number of sexual partners. Gonorrhea develops in about 25 percent to 50 percent of people exposed to a sexual partner with gonococcal infection. Gonococcal urethritis has a short incubation period ranging from two to ten days. There is no evidence that nonvenereal transmission is important in adults.

Asymptomatic gonococcal urethritis in men is a rare clinical problem. In a city public health clinic population only 0.9 percent to 1.5 percent of asymptomatic men at risk have cultures positive for gonococci, although some recent data suggest this frequency may be higher. This is in contrast to the greater than 80 percent prevalence of asymptomatic gonococcal infections of the pharynx and rectum and the mild nonspecific nature of gonococcal cervicitis. Sexual contacts of patients presenting with disseminated gonococcal infection should be evaluated for asymptomatic gonococcal urethritis, but screening urethral cultures for gonococci in all sexually active men is not recommended—independent of sexual orientation.

Nongonococcal urethritis is defined as the clinical syndrome of urethritis with negative urethral cultures for gonococci (nonspecific or postgonococcal urethritis or pseudogonorrhea). In the developed world nongonococcal urethritis appears to be twice as common as gonococcal urethritis and therefore more likely to be encountered in practice. In the United States nongonococcal urethritis is more likely to be seen in socially advantaged populations—whites, suburbanites, college students—in contrast to gonococcal urethritis. There is no evidence to support a racial susceptibility to one kind of urethritis or another. The incubation period of nongonococcal urethritis ranges from 2 to 35 days.

During the past ten years great strides have been made in defining the etiologic agents of nongonococcal urethritis. *Chlamydia trachomatis* causes an estimated 30 percent to 50 percent of cases of nongonococcal urethritis. In one study *C trachomatis* was cultured from 42 percent of 113 men with nongonococcal urethritis but in only 7 percent of 58 male controls without overt

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TABLE 1.—*Diagnosis of Urethritis*

Gram's Stain Result	*Diagnosis*	*Obtain Culture for Gonococci*	*Treatment*
Typical Gram-negative diplococci in the cytoplasm of polymorphonuclear leukocytes	Gonococcal	No	Recommended regimens
No Gram-negative diplococci in any location	Nongonococcal	No	Tetracycline/erythromycin
Equivocal findings	Gonococcal or nongonococcal	Yes	Tetracycline

urethritis. Serologic conversion in culture-positive cases and clinical response to specific antimicrobials have provided further support for *Chlamydia*'s etiologic role.

Another organism implicated as a possible cause of nongonococcal urethritis is *Ureaplasma urealyticum*. In two studies it was cultured in 80 percent of men with *Chlamydia*-negative nongonococcal urethritis; however, in 60 percent of an asymptomatic control group *U urealyticum* also was recovered. Although this difference is statistically significant, a major problem in assigning *U urealyticum* an etiologic role in nongonococcal urethritis is its ubiquity in asymptomatic controls. However, most experts agree that *U urealyticum* may cause nongonococcal urethritis and should be considered in treating this syndrome.

Although several other infectious agents have been postulated as causes of urethritis, none is considered to play a major role. *Trichomonas vaginalis* has been recovered on occasion from symptomatic men but it may represent a coincidental finding. An endourethral chancre of primary syphilis rarely may present as a urethritis syndrome. The common misconception that nongonococcal urethritis is due to excessive alcohol intake or to emotional upset should be discarded.

Clinical Presentation

Urethritis presents with one of two cardinal symptoms: (1) urethral discharge varying in quantity from a small bead of moisture at the meatus to a copious amount sufficient to stain a patient's underpants; (2) dysuria, which is defined as pain or discomfort in the anterior urethra characteristically exacerbated by urination. This discomfort frequently persists between micturition as pain, itching and frequency or urgency of urination, but hematuria and pain on ejaculation are distinctly uncommon. Since urine may clear the urethra of a slight discharge, examination should be carried out at least two hours after urination for optimal yield. If a spontaneous discharge is not apparent, stripping the urethra results in an exudate in more than 90 percent of remaining cases of urethritis.

Gonococcal urethritis presents most commonly with dysuria *and* a copious, spontaneous purulent discharge. In contrast, nongonococcal urethritis is more likely to present with dysuria *or* discharge, with as many as 20 percent of patients having no expressible discharge despite penile stripping. When a discharge is found it is more often mucoid than purulent and small in quantity. Since nongonococcal urethritis tends to be a milder clinical syndrome the majority of patients present more than four days after the onset of symptoms; the opposite is seen with gonococcal urethritis. In both gonococcal and nongonococcal urethritis local complications include epididymitis, prostatitis and urethral stricture; systematic complications may manifest as disseminated gonococcal infection or Reiter's syndrome.

Diagnosis

The differentiation of gonococcal and nongonococcal urethritis on clinical characteristics alone is difficult. A Gram's stain of the urethral discharge provides a simple, unequivocal, inexpensive and rapid method of differential diagnosis in most cases (see Table 1). Findings from a Gram's stain of a urethral discharge are abnormal if at least four polymorphonuclear leukocytes are seen per high-power field.

When typical Gram-negative diplococci are found within the cytoplasm of polymorphonuclear leukocytes, this is diagnostic of gonococcal urethritis. In large series this finding correctly identifies 90 percent of gonococcal urethritis cases and this Gram's stain finding has a positive predictive value of 98 percent using a positive culture as the gold standard. It is recommended, therefore, that therapy for gonococcal urethritis be instituted on the basis of this Gram's stain finding alone without carrying out an initial culture. A follow-up test-of-cure culture is recommended in all these patients.

A Gram's stain of urethral exudate showing *no* Gram-negative diplococci in *any* location (intracellular or extracellular) excludes gonococci as the cause of urethritis in 98 percent of cases. Routinely culturing for *N gonorrhoeae* in this situation is not recommended and appropriate therapy for nongonococcal urethritis should be initiated.

Results of a Gram's stain of urethral exudate are equivocal when it shows typical Gram-negative diplococci in an extracellular location only or atypical pleomorphic Gram-negative diplococci in any location. This situation requires further evaluation by culture in order to exclude a gonococcal cause. In one series 25 percent of 65 Gram's stains that gave equivocal findings were culture positive for *N gonorrhoeae*. Thus it is recommended that in equivocal cases cultures for gonococci be obtained and empiric therapy with a tetracycline be initiated.

The excellent sensitivity and specificity of Gram's stains as a diagnostic test in urethritis are derived from sexually transmitted diseases clinics. In the office setting where a Gram's stain may be done infrequently these characteristics of the test may not hold true. As a result a greater number of equivocal findings on Gram's stains requiring culture for gonococci is to be expected in

TABLE 2.—*Treatment of Urethritis—Summary of Adequate Drug Regimens*

Drug Regimen	*Gonococcal Urethritis*	*Penicillinase-Producing* Neisseria gonorrhoeae	Chlamydia trachomatis	Ureaplasma urealyticum	*Incubating Syphilis*
Aqueous procaine penicillin G 4.8 million units IM + probenecid 1 gram orally	Yes	No	No	No	Yes
Ampicillin 3.5 grams or Amoxicillin 3.0 grams + probenecid	Yes	No	No	No	Yes
Spectinomycin 2 grams IM	Yes	Yes	No	Partly effective	No
Tetracycline 2 grams for five days	Yes	50% Failures	Yes*	Yes*	Probably effective
Erythromycin 2 grams for five days	25% Failures	Unknown	Yes*	Yes*	No
Trimethoprim-sulfa 9 single-strength tablets for three days	Yes	Yes	Yes*	No	No
Cefoxitin 2 grams IM + probenecid	Yes	Yes	No	No	Probably effective
Cefotaxime 1 gram IM	Yes	Yes	No	No	Probably effective

*Treatment required for 7 to 14 days.

situations where there is less experience with the test.

Urethral specimens for cultures for *N gonorrhoeae* should be obtained with a calcium alginate swab inserted at least 2 cm into the urethra. For optimal yield this should be immediately plated on a modified Thayer-Martin medium. Cotton swabs are very uncomfortable and cotton may be toxic to some strains of *N gonorrhoeae.*

Isolation of *C trachomatis* requires tissue culture that is not readily available. In addition, it is expensive and results are usually delayed for about a week. Serologic diagnosis can be made retrospectively with the sensitive microimmunofluorescent techniques, but these have similar disadvantages to tissue culture. Given the currently available methods it is not practical to culture routinely for either *C trachomatis* or *U urealyticum.* Thus the diagnosis of nongonococcal urethritis is based on the exclusion by Gram's stain and culture of gonococcal causes; serology or other cultures to confirm this diagnosis are not recommended.

Therapy

The treatment of urethritis is summarized in Table 2.

The choice of drug regimen for uncomplicated gonococcal urethritis is primarily determined by the presence or absence of a history of penicillin allergy. Probenecid should be administered with each of the penicillin regimens in order to attain adequately high levels of penicillin. All of the listed regimens are equally effective for gonococcal urethritis but variably effective for coexistent pharyngeal and rectal *N gonorrhoeae.*

Penicillinase-producing *Neisseria gonorrhoeae* (PPNG) has been reported since 1975. It now constitutes a major problem in several Asian countries and may soon have a worldwide impact. In the United States its prevalence remains at less than 1 percent in most states, with most cases linked to contacts in East Asia. From 1979 to 1981 the number of reported cases caused by penicillinase-producing *Neisseria gonorrhoeae* increased ninefold with localized outbreaks in Los Angeles and Miami. In order to maintain adequate surveillance of such cases in the United States it is recommended that (1) all cases of gonococcal urethritis have a test-of-cure culture three to seven days after completion of antimicrobial therapy and (2) all treatment failures of gonococcal urethritis be confirmed by culture, checked for penicillinase production and treated with an effective regimen for penicillinase-producing *Neisseria gonorrhoeae.* Recommended antimicrobial regimens for this type of urethritis include the following: spectinomycin, 2 grams intramuscularly; trimethoprim-sulfa, 9 single-strength tablets a day for three days, or cefoxitin, 2 grams intramuscularly plus probenecid, 1 gram orally. Tetracycline is effective in only 50 percent of penicillinase-producing *Neisseria gonorrhoeae* infections and it is not recommended as empiric treatment. The third generation cephalosporins are effective in the therapy of gonococcal infections including penicillinase-producing strains. At this time the only patients with gonococcal urethritis who should be empirically treated with an effective regimen for penicillinase-producing strains are (1) contacts to a known case of infection with these strains and (2) cases following recent sexual contacts in East Asia.

Treatment of nongonococcal urethritis is empiric and based on exclusion of a gonococcal cause. Tetracycline given for at least seven days will cure 80 percent of *C trachomatis* urethritis and 70 percent of presumed *U urealyticum* urethritis. Erythromycin is effective against both *C trachomatis* and *U urealyticum* but it has a 25 percent failure rate against gonococcal urethritis. Sulfonamides are effective for *C trachomatis* urethritis but ineffective against *U urealyticum.* Penicillin is effective against neither *C trachomatis* or *U urealyticum.* Thus 2 grams of tetracycline per day for seven days is the recommended therapy for nongonococcal urethritis. A regimen of 2 grams of erythromycin per day for seven days is recommended as an alternative for tetracycline intolerant patients and cases of treatment failure. In up to 30 percent of patients with nongonococcal urethritis, therapy will fail or relapse will occur within seven weeks; a second course of antimicrobials and sympathetic follow-up by the primary care physician will be needed.

It is imperative to treat the sexual contacts of cases with gonococcal urethritis with appropriate antimicro-

bial drugs regardless of the presence or absence of symptoms. The treatment of sexual contacts of cases with nongonococcal urethritis is as yet an unresolved issue. Correct use of condoms has been reported to protect men from gonococcal urethritis but this assumption cannot be made in treating case contacts. It is the physicians' responsibility to pursue contact tracing with the cooperation of patients and the assistance of public health departments.

Summary

Urethritis is a frequently encountered clinical problem with an important differential diagnosis. Gram's stain of urethral discharge can determine its cause quickly in many cases; culture for gonococci provides complementary information in cases with equivocal Gram's stain findings. Therapy for gonococcal urethritis is effective with any of several regimens but special attention should be given to possible infections with penicillinase-producing *Neisseria gonorrhoeae*. Nongonococcal urethritis is best treated with tetracycline or erythromycin. All sexual contacts of patients with urethritis of any cause need to be evaluated and treated.

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